

Survival among patients with lung cancer managed at a tertiary care center in North India

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Abstract

Though there has been advancement in the management of lung cancer, it is not well utilized due to its limited availability and high cost. This is a prospective observational study done at a tertiary care center from January 2014 to December 2022, involving patients with primary lung cancer. After tumor-node-metastasis staging and molecular testing, the patients received chemotherapy, radiotherapy, surgery, targeted therapy, and immunotherapy in various combinations as per the prevailing National Comprehensive Cancer Network Guidelines. A total of 92 patients were enrolled in the study, with a mean age of 58.94±10.33; 72 (78.26%) were males. 69 (75%) patients were either current or former smokers. 78 (84.78%) patients had an Eastern Cooperative Oncology Group (ECOG) score of 0-2, while the remaining had an ECOG of 3-4. 80 (86.95%) patients had non-small cell lung cancer (NSCLC) [44 (47.83%) adenocarcinoma, 25 (27.17%) squamous cell carcinoma, and 11 (11.95%) NSCLC: not otherwise specified], while 12 (13.04%) patients had small cell lung cancer. One (1.08%) patient each presented in stage I and stage II, 31 (33.69%) patients presented in stage III, and 59 (64.13%) patients presented in stage IV. 44 patients with adenocarcinoma were subjected to mutational analysis, and an epidermal growth factor receptor mutation was found in 13 (29.5%) patients. None of the patients had an ALK mutation, ROS-1 rearrangement, or BRAF mutation. PD-L1 expression was evaluated in 9 patients with NSCLC, and it was found in 6 (66.66%) patients. The overall mean survival was 12.7 months. The mean survival for patients with stages I, II, III, and IV was 70, 96, 8.1, and 12.7 months, respectively. Survival in stage IV was better than in stage III, as the eligible patients received targeted therapy and immunotherapy. Targeted therapy and immunotherapy have improved survival. Molecular analysis should be done whenever indicated, and eligible patients must be administered targeted therapy and immunotherapy.

Introduction

Lung cancer is the most frequently diagnosed cancer and accounts for the maximum number of cancer-related mortality worldwide [1]. In India, lung cancer comprises 5.9% of all cancers and 8.1% of cancer-related mortality [2]. There has been a recent advancement in the management of lung cancer, which has moved from the treatment determined by histopathology and immunohistochemistry to the treatment determined by mutation analysis and biomarker expression. Besides conventional chemotherapy and radiotherapy, the management of lung cancer involves targeted therapies and immunotherapy. This involves a huge economic burden from both diagnostic and treatment points of view. Health services in our country are provided by the public and private sectors [3]. The private health system is unaffordable for most patients, and they even-

tually turn to the public health system. These public health systems are often overburdened and lack suitable infrastructure. Though our institute comes under the public health system, patients here are insured and are optimally managed according to the prevailing guidelines. Thus, the patients treated by us, *i.e.*, the Employee State Insurance Corporation, do not face the economic challenge. The results of the treatment thus represent if ideal circumstances are provided to Indian patients what is the likely result. It can guide us on whether the economic challenges are worth taking up. This study was undertaken to study the overall survival of patients with primary lung cancer who were optimally managed as per the available recommendations.

Materials and Methods

The study was conducted in the Department of Pulmonary and Critical Care Medicine, ESI-PGIMS, Basaidarapur, New Delhi. It is an observational prospective study conducted among patients diagnosed with primary lung cancer, irrespective of their age and gender. The patients who consented to participate during the study period from January 2014 to December 2021 were included in the study. Ethical clearance was obtained from the institutional ethical committee.

The study included those patients who presented with a lung nodule, lung mass, consolidation, and large effusions that were histologically or cytologically confirmed as primary lung cancer. The clinical history, sociodemographic history, family history, smoking history (type and number smoked, duration of smoking, exposure to environmental tobacco smoke or biomass fuel), and past history were recorded. Blood was sent for a complete hemogram and biochemical tests. For patients with pleural effusion, pleural fluid was sent for cell counts, biochemical tests, cytology, and adenosine deaminase levels. The patients were evaluated radiologically with a chest radiograph and contrast-enhanced computed tomography (CECT) scan of the thorax. When indicated, a magnetic resonance imaging with contrast or CECT scan of the brain was done. The diagnosis was established by various procedures, including computed tomography (CT) guided or ultrasound guided transthoracic fine needle aspiration cytology and biopsy for peripheral tumors, fiberoptic bronchoscopy wash, brush or biopsy, and transbronchial needle aspiration for central tumors and closed pleural or thoracoscope guided pleural biopsy for patients presenting with pleural effusions or a combination of various procedures. Whole body positron emission tomography-CT was done for staging the disease. The staging was done according to the tumor-node-metastasis (TNM) staging system by the American Joint Committee on Cancer staging system. The 7th edition of TNM staging was used for patients diagnosed by December 31, 2016, and the 8th edition was used thereafter [4,5]. Molecular testing was done to ascertain the presence of a driver mutation for patients with histopathology of adenocarcinoma. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutation analysis has been recommended and available since the inception of our study. c-ROS oncogene 1 (ROS-1) rearrangement and v-raf murine sarcoma viral oncogene homolog B (BRAF) mutation were also tested following the recommendation for the same in 2018 [6]. However, prevailing guidelines did not suggest the use of biomarkers for squamous cell carcinoma, so it was not done for all the patients. Similarly, programmed cell death ligand 1 (PD-L1) testing was done once it was recommended and became available in our country. The patients were treated with surgery, chemotherapy, radiotherapy, chemoradiotherapy, targeted therapy, or immunotherapy in various combinations and sequences as per the prevailing National Comprehensive Cancer Network guidelines. The management was

decided through a multidisciplinary discussion, which involved the pulmonologist, medical oncologist, surgical oncologist, radiation oncologist, pathologist, and radiologist. Those deemed unfit for these therapies were given palliative treatment and the best supportive care. A total of 92 patients were enrolled in the study, and the data were analyzed 1 year after the end of the study period.

Results

A total of 92 patients with lung cancer were enrolled in the study and were followed up for at least 1 year following the study period. The baseline characteristics of the lung cancer patient are shown in Table 1. The mean age of the study population was 58.94±10.33. 72 (78.26%) were male and 20 (21.74%) were female. 69 (75%) patients were current or former smokers. Chronic obstructive pulmonary disease (COPD) was the most common comorbidity found in 34 (36.95%) patients. Coronary artery disease, diabetes mellitus, and hypertension were found in 1 (1.08%) patient, 5 (5.43%) patients, and 6 (6.52%) patients, respectively. Eastern Cooperative Oncology Group (ECOG) performance status scale was 0-2 in 78 (84.78%) patients, while it was 3-4 in 14 (15.22%) patients.

The type, stage, and molecular characteristics of lung cancer are shown in Table 2. 80 (86.95%) patients had non-small cell lung cancer (NSCLC), while 12 (13.04%) patients had small cell

Table 1. Baseline characteristics of lung cancer patients.

Parameters	(n=92)
Age	58.94±10.33
Gender M: F (M%)	72: 20 (78.26)
Smoker, n (%)	69 (75)
Pack year (smoking)	25.69±20.14
Comorbidities, n (%)	48 (52.17)
Diabetes mellitus	5 (5.43)
Hypertension	6 (6.52)
Chronic obstructive airway disease	34 (36.95)
Coronary artery disease	1 (1.08)
ECOG 0-2, n (%)	78 (84.78)
ECOG 3-4, n (%)	14 (15.22)

M, male; F, female; ECOG, Eastern Cooperative Oncology Group.

Table 2. Type, stage and molecular characteristics of lung cancer.

Parameters	(n=92) n (%)
Adenocarcinoma	44 (47.83)
Squamous cell carcinoma	25 (27.17)
NSCLC NOS	11 (11.95)
Small cell carcinoma	12 (13.04)
Stage I	1 (1.08)
Stage II	1 (1.08)
Stage III	31 (33.69)
Stage IV	59 (64.13)
EGFR (n=44)	13 (29.5)
ALK	0
PD-L1 (n=9)	6

NSCLC NOS, non-small cell lung cancer not otherwise specified; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, programmed cell death ligand 1.

lung cancer. Among NSCLC patients, 44 (47.83%) patients had adenocarcinoma, 25 (27.17%) patients had squamous cell carcinoma, and 11 (11.95%) patients had NSCLC: not otherwise specified. The presentation was in stage I and stage II in 1 (1.08%) patient each. 31 (33.69%) patients presented in stage III, while 59 (64.13%) patients presented in stage IV. 44 patients of adenocarcinoma were subjected to mutational analysis, and an EGFR mutation was found in 13 (29.5%) patients. PD-L1 expression was evaluated in 9 patients with NSCLC, and it was found in 6 (66.66%) patients.

The overall survival rate, stage-wise survival at 6 months and 1 year, and mortality by 1 year are depicted in Table 3. The 6-month and 1-year survival rates were 58 (63.04%) and 37 (40.21%), respectively. The mortality within 1 year of diagnosis was 54 (58.69%). Stage III and stage IV mortality rates within a year were 38.89% and 61.11% respectively. While 2-year and 3-year survival rates were 13 (14.13%) and 7 (7.60%), respectively.

Out of 58 patients who survived beyond 6 months, 1 (1.72%) patient each belonged to stage I and stage II, 20 (34.48%) patients belonged to stage III, and 36 (62.06%) patients belonged to stage IV. Among 38 patients who survived beyond 1 year, 1 (2.63%) patient each belonged to stage I and stage II, 10 (26.31%) patients belonged to stage III, and 26 (68.42%) patients belonged to stage IV.

In 54 cases (58.69%), mortality was recorded within a year of treatment. Although no mortality was recorded in stage I and stage II, 21 (38.88%) patients with stage III disease and 33 (61.11%) patients with stage IV disease died within a year of the disease.

Lung cancer patients with survival for at least 1 year or more were compared to such patients with mortality within a year (Table 4). Patients were relatively younger in the former group. The mean age of the patient was 55.18±10.35 years in those who survived for more than 1 year and 61.59±9.55 years in those who did not; the difference was statistically significant ($p=0.001$). The male-to-female ratio was 31:7 and 41:13 in the former and latter groups, respectively. Though statistically insignificant, more patients in the latter group were either current or former smokers [42 (77.78%) vs. 27 (71.05%); $p=0.463$], with relatively higher pack years of smoking (27.16±19.18 vs. 23.60±21.5; $p=0.203$). Prevalence of comorbidities was also high in the latter group in comparison to the former group [30 (55.56%) and 18 (47.36%),

respectively; $p=0.438$]. ECOG performance status scale was 0-2 and 3-4 for 36 (94.73%) and 2 (5.26%) lung cancer patients, respectively, who survived for more than 1 year while it was 0-2 and 3-4 for 42 (77.78%) and 12 (22.22%) lung cancer patients respectively who died within 1 year of diagnosis.

Among 38 lung cancer patients who survived for 1 year or more, 20 (52.63%) had adenocarcinoma, 10 (26.31%) had squamous cell carcinoma, 4 (10.52%) had NSCLC not otherwise specified (NOS), and 4 (10.52%) had small cell lung cancer. Among 54 lung cancer patients who died within 1 year, 24 (44.44%) had adenocarcinoma, 15 (27.78%) had squamous cell carcinoma, 7 (12.96%) had NSCLC NOS, and 8 (14.81%) had small cell lung cancer. 9 (23.68%) patients with EGFR mutation survived for more than 1 year, while 4 (7.41%) patients died within 1 year. 4 (10.52%) patients with PD-L1 expression survived for more than 1 year, while 2 (3.70%) patients died within 1 year.

Table 3. Overall survival rate, stage-wise survival at 6 months and 1 year, and mortality within a year.

Overall survival rate, n (%)	
6-month survival	58 (63.04)
1-year survival	38 (41.30)
2-year survival	13 (14.13)
3-year survival	7 (7.60)
Mortality within 1 year	54 (58.69)
Stage wise survival ≥ 6 months (n=58), n (%)	
Stage I	1 (1.72)
Stage II	1 (1.72)
Stage III	20 (34.48)
Stage IV	36 (62.06)
Stage wise survival ≥ 1 year (n=38), n (%)	
Stage I	1 (2.63)
Stage II	1 (2.63)
Stage III	10 (26.31)
Stage IV	26 (68.42)
Stage-wise mortality within 1 year (n=54), n (%)	
Stage I	0
Stage II	0
Stage III	21 (38.89)
Stage IV	33 (61.11)

Table 4. Comparison between patients who survived for more than a year vs. patients who had mortality within a year.

Parameters	Patients survived ≥ 1 year (38)	Mortality within 1 year (54)	p
Age	55.18±10.35	61.59±9.55	0.001
Gender M: F	31: 7	41: 13	0.517
Smoker, n (%)	27 (71.05)	42 (77.78)	0.463
Pack year (smoking)	23.60±21.5	27.16±19.18	0.203
Adenocarcinoma, n (%)	20 (52.63)	24 (44.44)	0.43
Squamous cell ca, n (%)	10 (26.31)	15 (27.78)	0.88
NSCLC NOS, n (%)	4 (10.52)	7 (12.96)	0.72
Small cell carcinoma, n (%)	4 (10.52)	8 (14.81)	0.55
EGFR, n (%)	9 (23.68)	4 (7.41)	0.027
PD-L1, n (%)	4 (10.52)	2 (3.70)	0.191
ECOG 0-2, n (%)	36 (94.73)	42 (77.78)	0.025
ECOG 3-4, n (%)	2 (5.26)	12 (22.22)	

M, male; F, female; ECOG, Eastern Cooperative Oncology Group; NSCLC NOS, non-small cell lung cancer not otherwise specified; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, programmed cell death ligand 1.

Sub-group analysis was done to compare the patients of adenocarcinoma with and without EGFR mutation (Table 5). The age of the patients was comparable in both groups. The mean age was 58.38±11.8 years in those with EGFR mutation and 58.93±11.19 years in those without EGFR mutation. Only 2 (15.4%) patients were smokers in the group with EGFR mutation, while 22 (70.9%) patients were smokers in the group without EGFR mutation, which was statistically significant ($p=0.0007$). The mean survival was 22.07±1.81 months in the mutation group, while it was 12.2±1.83 months in the non-mutation group ($p=0.0001$).

The mean survival of patients with lung cancer is depicted in Table 6. Mean survival for patients with stage I, stage II, stage III, and stage IV was 70, 96, 8.1, and 12.7 months, respectively. Overall mean survival was 12.7 months. Mean survival among patients with adenocarcinoma, squamous cell carcinoma, NSCLC: NOS, and small cell lung cancer was 14.9, 12.4, 11.1, and 6.8 months, respectively.

Discussion

In this study, the mean age of patients with lung cancer was 58.9 years. This was similar to various studies conducted in India [7-10], but it is earlier than the mean age reported in Western countries [11-

13]. The mean age of presentation has largely remained unchanged over the past several years. Many of the patients in our study were male, which is in line with other Indian studies [9,10,14-17]. Besides smoking habits and occupational exposure, this may be because males tend to seek medical attention more frequently and promptly than females in our society [12,13,18-20]. However, the prevalence among males was higher than in Western countries, possibly because of the higher prevalence of smoking among men in India. A total of 69 (75%) patients in our study were smokers, which is again comparable to various Indian studies [9,10,21,22], while the smoking prevalence varies between 87% and 93% in Western countries [11,19,20]. COPD was the most common comorbidity in our study since smoking is a risk factor for both COPD and lung cancer.

The ECOG performance status scale was grossly preserved in most patients. It was 0-2 in 78 (84.78%) patients while it was 3-4 in 14 (15.22%) patients. This may be owing to the patient presenting to us whose vocation involves physically strenuous activities. Though it was better than the other Indian studies, it was still lower than the Western reports [23-25]. Though squamous cell carcinoma was the most common histology in older studies, adenocarcinoma is the most common lung cancer in recent studies [9,21,22,26]. This was also evident in our study, where 44 (47.8%) patients had adenocarcinoma, while 25 (27.2%) patients had squamous cell carcinoma.

Table 5. Comparison between patients of adenocarcinoma with and without EGFR mutation.

Parameters	Adenocarcinoma with EGFR mutation (n= 13)	Adenocarcinoma without EGFR mutation (n=31)	p
Age	58.38±11.8	58.93±11.19	0.441
Gender M: F	9: 4	24: 7	0.567
Smoker	2	22	0.0007
Pack year (smoking)	6.36±14.33	34.22±12.86	<0.00001
ECOG 0-2	12	27	0.619
ECOG 3-4	1	4	
Survival (mean±SD in months)	22.07±1.81	12.2±1.83	0.0001

EGFR, epidermal growth factor receptor; M, male; F, female; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table 6. Mean survival of lung cancer patients.

Category	Mean survival (months)
Stage I	70.0
Stage II	96.0
Stage III	8.1
Stage IV	12.7
Overall mean survival	12.7
Mean survival of SCLC	6.8
Mean survival of NSCLC	13.6
Mean survival of adenocarcinoma	14.9
Mean survival of squamous cell carcinoma	12.4
Mean survival of NSCLC: NOS	11.1
EGFR-positive adenocarcinoma	22.0
EGFR-positive NSCLC	22.0
EGFR-negative adenocarcinoma	12.2
Mean survival of stage IV patients, excluding EGFR-positive patients	9.9
Mean survival of stage IV patients, excluding EGFR-positive patients and patients who received immunotherapy	8.4

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; NSCLC NOS, non-small cell lung cancer not otherwise specified; EGFR, epidermal growth factor receptor.

ma. The prevalence of small-cell lung cancer has been similar to recent studies across the globe.

Lung cancer is notoriously known to present in an advanced stage of the disease [27,28]. This was evident in our study as well, where the presentation was in stage I and stage II in 1 (1.08%) patient each. While 31 (33.69%) patients presented in stage III, 59 (64.13%) patients presented in stage IV. This finding was similar to various studies from different parts of India [23]. Only 3.2% of our patients underwent surgery, which was similar to other studies from India [23]. The plausible explanation may be the fact that the symptoms are similar to other common diseases. Many of the patients are treated for pleuro-pulmonary tuberculosis before being referred to the specialist for evaluation for non-response to the treatment administered. Some of the patients attribute the symptoms to ageing and comorbidities like COPD and CAD. So, overall, we need to step up our surveillance. Primary care physicians should be trained to have a high index of suspicion for the diagnosis of lung cancer so that it can be diagnosed at an early stage, and hence, survival will improve.

A total of 44 patients with adenocarcinoma were subjected to mutational analysis, and an EGFR mutation was found in 13 (29.5%) patients. This was comparable to most of the Indian studies but was higher than the findings from the Western world [29-36]. Surprisingly, none of the patients were found to harbor ALK mutation, ROS-1 rearrangement, or BRAF mutation. The patients exhibiting EGFR mutation were treated with targeted therapies. 9 (69.2%) patients survived for 1 year or more, while 4 (30.7%) patients died within 1 year of treatment, and this was found to be statistically significant ($p=0.027$). PD-L1 expression was evaluated in 9 patients with NSCLC, and it was found positive in 6 (66.66%) patients. These patients received pembrolizumab as a part of their treatment regimen.

Limited data on lung cancer survival is available for the Indian population. In this study, the overall survival of the lung cancer patient was evaluated. The mean overall survival in our study was 12.7 months, and it was higher than various studies reported from our country [37-39]. The mean survival for patients with stage III lung cancer was 8.1 months. Surprisingly, the mean survival for patients with stage IV lung cancer was 12.7 months. However, these patients with stage IV lung cancer also included eligible patients who received targeted therapies and immunotherapy, and hence, they had better survival. The mean survival for stage IV patients who received conventional chemotherapy (*i.e.*, patients who were not eligible for either targeted therapies or immunotherapy) was only 8.4 months. So basically, survival improved significantly due to the administration of targeted therapies and immunotherapy to the stage IV patients who were eligible for the same. Similar to this, Garg *et al.* have also described better overall survival for patients receiving targeted therapy [40].

Mean overall survival was enhanced in patients exhibiting EGFR mutations. The mean survival was 22.07 ± 1.81 months in patients with adenocarcinoma with EGFR mutation, while it was 12.2 ± 1.83 months in patients without EGFR mutation ($p=0.0001$; 95% confidence interval 8.65 to 11.09). This implies that targeted therapies have significantly improved survival in patients with adenocarcinoma exhibiting EGFR mutations. This further emphasizes evaluating a patient for mutational analysis so that targeted therapy can be administered. Though we have treated eligible patients with targeted therapy, this was not the case in other studies from our country because of cost constraints. Unlike our patients, their patients were not covered by insurance, hence only 50% of the eligible patients received targeted therapy [40]. Most of our patients

who were eligible for targeted therapy were treated with osimertinib, which was available to them free of cost, but for a non-insured person, it would cost lakhs.

Conclusions

Our study highlights a few necessary points regarding the management of lung cancer. Diagnostic and staging modalities and facilities for mutation analysis help in the better management of lung cancer. They should be available in all the referral centers. Targeted therapies improve the survival of lung cancer patients. In our country, these drugs are not available at subsidized cost. Poor patients are not able to avail these advancements. Therefore, costs incurred in the management of lung cancer should be subsidized.

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